ENVIRONMENTALLY BENIGN SYNTHESIS OF SOME BIODYNAMIC HETEROCYCLES

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1. INTRODUCTION

The 'greening' of global chemical processes has become a major issue in the chemical industry. With the increasing interest in human health and environmental protection ideal industrial chemical processes require energy saving, high conversion, high selectivity and solvent free reaction conditions with minimising the processes themselves. Industrial chemistry in the new millennium is widely adopting the concept of "Green Chemistry" to meet the fundamental scientific challenge of protecting the human health and environment while maintaining commercial profitability.[1,2] The demand for diverse compound libraries for screening in drug discovery and material science is the driving force behind development of new technologies for rapid parallel and combinatorial synthesis.[3] One of those high-speed techniques is microwave assisted solvent-free approach, which has recently got momentum because of its environmentally friendly nature and cost effectiveness.

Environmentally friendly synthesis of organic compounds without using organic solvents has come several steps closer in recent years. Strict environmental legislations have forced scientists all over the world to develop alternative syntheses of biologically and synthetically important compounds. Solvent free synthesis generally refers to absence of solvents in the synthetic step itself; however, a considerable amount of solvent is used in adsorption of reagents and elution of the product which lessens the environmentally benign approach. Neat reactions on the other hand have their own practical problems such as overheating and charring of compounds due to ineffective dissipation of energy etc. However, coupling of solvent less synthesis with microwaves shown benefits of shorter reaction times, uniform heating and higher yields.[4,5]

In recent years, with the increasing interest in human health and environmental protection, the need for clean and easily recycled reagents in organic synthesis has meant that solid-supported reagents and scavengers have received more and more attention from organic chemists. Compared to the traditional solution phase reactions, the use of solid-supported and scavengers simplifies the work-up operations by allowing simple filtration, and avoids release of excess

reactants or by-products in to the environment.[6] Furthermore, the reclaimed solid supported reagents and scavengers can be reused rough simple regeneration in most cases.

A microwave heating technique should be promising candidate; replacing conventional boilers because microwave-assisted organic syntheses can lead to large reductions in reaction time and to enhancement in conversion and selectivity compared to conventional heating.[7] These microwave effects could be attributed to the characteristic heating modes of microwave through the interaction of oscillating electric and magnetic fields with ordered assemblies of polar molecules expressed as dielectric loss, leading to unusual phenomena called superheating or hot-spots. Further organic reactions in water without using harmful organic solvents have attracted a great deal of interest in both academic and industrial research because, in addition to environmental concerns, there are beneficial effects of aqueous solvents on rates and selectivities of important organic transformations.[8]

The study of heterocyclic systems provides the most fascinating field for exploration, in view of the variety of interesting and intricate reactions which lead to the synthesis of unusual systems having diversities in their skeletal pattern. Heterocyclic compounds are well recognized for their multifaceted pharmacological and biochemical behaviour and as far as their relationship to medicinal chemistry is concerned the two areas are almost inseparable.[9]

Among them, sulphur and nitrogen containing heterocyclic compounds have maintained the interest of research as their unique structures led to several applications in different areas.[10] The incorporation of fluorine in heterocyclic systems, particularly at critical reaction sites with specific stereochemistry, has received considerable attention as this may produce far reaching changes in the biological activities of heterocycles.[11]

The synthesis of heterocycles by conventional methods is orders of magnitude too slow to satisfy the demand for generation of such compounds. Obviously, these methods involve long reaction times, high temperatures, use large quantities of organic solvents and some give unsatisfactory yields. The synthetic chemical community has been under increased pressure to produce, in an environmentally benign fashion, the myriad of substances required by society in short periods of time, and the best option to accelerate these synthetic processes is to use microwave (MW) technology`. Synthesis of heterocycles is one of the most widely used areas in the microwave chemistry. In the microwave environment chemical reactions usually proceed

with high reaction rates, formation of cleaner products, and takes place with operational simplicity which give fewer by-products.[12,13] The reactions which are not possible under the conventional conditions can sometimes be affected by the high energy of Microwave irradiation.

In view of the wide range of biological activities associated with oxygen, nitrogen and sulphur containing heterocyclic compounds and our interest in non-conventional method of reaction activation and developing new economic and environmentally benign strategies, various heterocyclic systems have been synthesized by conventional heating and in the cavity of microwave oven under solvent free conditions.

2. PURPOSE OF STUDY

In the past few decades, many significant advances in organic chemistry such as novel synthetic strategies and methods as well as the advent of vast array of analytical apparatus and techniques have made the organic synthesis more dynamic and effective than ever before. However, the practical aspects for carrying out laboratory-scale reactions have changed little during this period. Especially when heating is necessary, oil baths and heating jackets are the main equipments used. These traditional heating techniques are slow and time-consuming and sometime can lead to overheating and decomposition of the substrate and product. In these environmentally conscious days, one of the main challenges to the chemical research has been to develop 'Clean and Efficient' technologies for chemical synthesis. The developments in technology are directed towards environmentally sound and cleaner procedures.

Hence, the present day's chemists are no longer confined to use only thermal energy for driving chemical reactions. With increasing complexity of problems and the availability of newer methods of activation of chemical reactions, chemists have resorted to use wide variety of techniques such as photochemical, electrochemical, microwave and enzymatic methods. With the easy availability of microwave sources, their popularity and synthetic utility in organic chemistry have increased considerably in recent years. Microwave provides a powerful way to do synthetic chemistry in the light of the current paradigm shift to "Green Chemistry".

Further, Heterocyclic chemistry has contributed significantly to our present knowledge of medicinal pharmaceutical chemistry and biochemistry. The study of heterocyclic system is one of the most fascinating fields for the organic chemistry. Heterocycles are essential to many life processes and compounds like vitamin, enzymes, polysaccharides, etc belong to the very essence of life. In contrast to the conventional method, the MW process offers new vistas, without the use of long range of glassware's to cleaner reactions products and enhanced yields. Encouraged by the vast potential of "Microwave Induced Organic Synthesis" and wide variety of biological activities associated with O, N and S containing heterocycles, the envisaged work has been undertaken as "**Environmentally Benign Synthesis of Some Biodynamic Heterocycles"**

3. LITERATURE SURVEY

Chemistry plays a major role in our environment. There are many chemical species in our environment, which cause large chemical phenomena. During the past decades, the environmental consciousness has compelled the chemists to make a new twist on an old theme.[14]

It is necessary for synthetic organic chemist to organize research in such a way that it preserves the environment and to develop procedures that are both environmentally and economically acceptable (Green chemistry procedures). One major objective therefore to simplify and accommodate in a modern way the classical procedures with the aim of keeping pollution effects to a minimum, together with a reduction in energy and raw materials consumption.

In this endeavour, solid supported reagents[14,15] have made a land mark and made significant contribution to preserve the green environment by reducing the waste effluents. With the development of microwave oven[16,17] reactions in dry media become easier to do as the high heating efficiency of microwave gives remarkable rate enhancement, higher yields, greater selectivity and ease of manipulation. In addition, the limitations of the microwave assisted reactions in solvents namely the development of high pressure and the need for specialized sealed vessels, circumvented via this solid support strategy, which enables organic reactions to occur rapidly at atmospheric pressures[18] and upscale the reaction on a preparative scale.

MW ranges from 1cm to 1m in in wavelength in the electromagnetic spectrum and are situated between the IR and radiofrequencies. There are two mechanisms associated with microwave heating: **dipole rotation and ionic conduction**.

The applications of microwaves to organic synthesis were first of all reported by Gedye et al.,[18] and Majetich et al.,[19] in 1986. A recent survey reveals that a large no. of publications have appeared on microwave mediated chemical reactions and subject is reviewed by many workers i.e. R.A. Abromovich[20] (1997); S. Caddick[21] (1995); Galema[22] (1997); Loupy et al.,[23] (1998); R.S. Varma[24] (1999, 2002) ; P. Lidstrom[25] (2001); Larhed[26] (2002); Hays[27] (2004) ; Kappe (2004); Nuchter[28] (2004) , Hoz[29] (2005), Li, Jianping[30] (2006), Landge[31] (2008).

Two types of reactors used for microwave assisted organic synthesis are:

(1) Multimode reactors (2) Monomode reactors

Domestic microwave ovens as multimode reactors are the most common instruments used in organic synthesis since they are comparatively inexpensive and readily available Using domestic microwave oven cavity, lots of satisfying organic syntheses have been done. However, the multimode reactors provide a field pattern with areas of high and low field strength, commonly referred to as "hot and cold spots." This non-uniformity of the field leads to the heating efficiency varying drastically between different positions of the sample but this problem can be solved by previous cartography.

The single mode cavity, as the name implies, allows only a single mode to enter the cavity by wave-guide. A properly designed monomode reactor can prevent the formation of "hot and cold spots". This advantage is very important in organic synthesis since the actual heating pattern can be controlled. Therefore, higher reproducibility and predictability are achieved. In addition, higher power levels can be obtained in single mode systems but the main limiting factor for these reactions is their very high cost and scale up of reaction is not possible.
This review collects the synthesis of different heterocycles. The synthesis of simple 5- and 6-membered N-, O-, and S-containing heterocycles have all been facilitated in recent years[32] with advent of new technology for microwave assisted synthesis.

In recent decades, there has been an explosion of activity in the chemistry of nitrogen containing heterocycles such as indole, thioxotriazinone, pyrazoles, trizole derivatives,

imidazoles, dihydropyrimidinones, etc deserve a special mention due to their versatile use in pharmacological and biochemical studies[33-45] because they not only display interesting chemistry as individual ring system but may also lead to a large number of new fascinating ring systems by incorporating more than one moiety leading to a variety of structural patterns.

The numbers of possible heterocyclic systems are practically unlimited as the ring can have varying size from three membered rings upwards and heteroatom can be drawn from a very large group of elements. Amongst the naturally occurring compounds, drug research heterocycles occupy an important position not only because of their wide spread distribution in the plant world, but also because of the fact that some novel approaches have converged into a distinctive discipline with the strategic objective being increased efficiency, sustainability and finally, social benefit and this discipline is that of 'clean chemistry' more commonly known as 'green chemistry'.

4. PROPOSED WORK

Since most of clinically important drugs available in the market are heterocycles thus keeping in view the immense medicinal importance of azaheterocyclic compounds as potential antiviral, antibacterial, antifungal, anti-inflammatory, antihypertensive, antitumor, antidepressants and so on, and in continuation of the ongoing work being carried out by our research group developing clean, efficient and economic procedures using microwaves the present work entitled **"Environmentally benign synthesis of some biodynamic heterocycles"** would be carried out with the aim to explore newer trends in the upcoming areas of "Green chemistry" by using microwave technology for devising alternative, clean, efficient, economic and environmentally benign methodology.

The present work will be carried out in following two parts.

(A) Synthesis

(B) Biological Screening

(A) Synthesis

Among the most promising ways to reach this goal, solvent free techniques hold a strategic position as solvents are often very toxic, expensive, and problematic to use and to remove. It is the main reason for development of such modern technologies. We propose to investigate the following research plan to synthesize some biodynamic heterocycles.

1. Investigation of the reaction of 1H-indole-2,3-dione with substituted thiosemicarbazide: Improved synthesis of thioxotriazinones, triazino indoles, Schiff bases and N-Mannich bases.
2. Investigation of reaction of aromatic aldehydes, 1,3-dicarbonyl compound with urea/thiourea/substituted thiourea in the presence of novel catalysts under solvent free condition.
3. Investigation of reaction of 1H- indole -2,3-dione with active methylene compounds.
4. Investigation of reaction of aromatic ketones with amino acids.
5. Investigation of reaction of substituted thiazoles with cyclic ketones.
6. Identification and characterization of the synthesized compounds using IR, ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and mass spectra.

(B) Biological Screening of the compounds:

A representative number of compounds will be screened for anti-fungal and anti-bacterial activities in Department of Microbiology, MITS University, Lakshmangarh, Rajasthan and anti-cancer activity in "Advanced Centre for Treatment, Research and Education in Cancer (ACTREC)" Kharghar, Navi Mumbai.

1. **Antifungal activity-** Compounds will be screened for antifungal activity against Alternaria alternata.
2. **Antibacterial activity-** Compounds will be screened for antibacterial activity against Escherichia coli, Staphylococcus aureus, K. pneumonia.
3. **Anticancer activity-** Compounds will be screened for anti cancer activity against the cell lines "Human Lung Cancer (A549)" and "Human Breast Cancer (MCF7)".

5. WORK ALREADY DONE

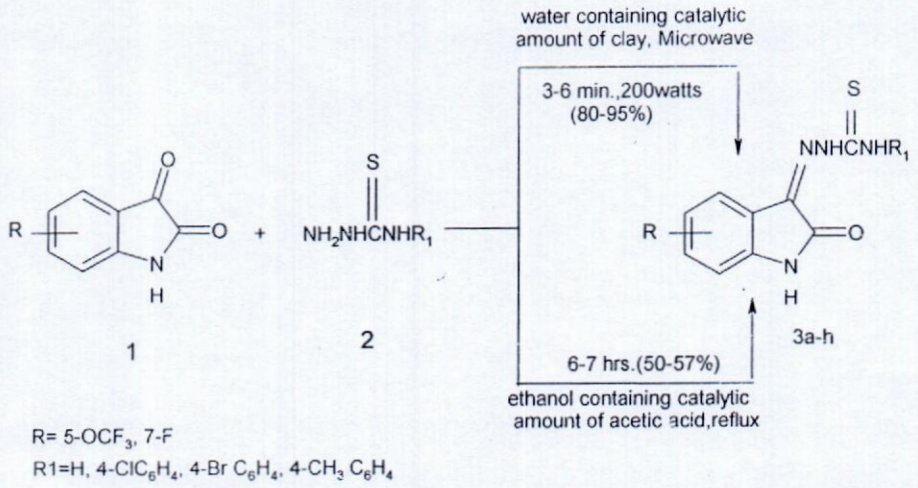
1. Investigation of the reaction of 1H-indole-2, 3-dione with substituted thiosemicarbazide: Improved synthesis of thioxotriazinones, triazino indoles, Schiff bases and N-Mannich bases.

The work has been divided into three parts:

(I) Aqua mediated facile synthesis of substituted hydrazine carbothioamides (schiff's bases) under microwave irradiation.

In continuation to our interest on use of aqueous medium for heterocyclic synthesis, we report herein for the first time the microwave promoted, economic, ecofriendly, and facile synthesis of 2-(5/7-fluorinated-2-oxoindolin-3-ylidene)-N-(4-substitutedphenyl)hydrazine

carbothioamides **3** by the reaction of 5/7- fluorinated 1H-indole-2, 3-diones **1** and 4-substituted (Cl/Br/CH3) phenyl thiosemicarbazide **2** in aqueous medium containing catalytic amount of montmorillonite K10 clay under microwave irradiation (Scheme-I).



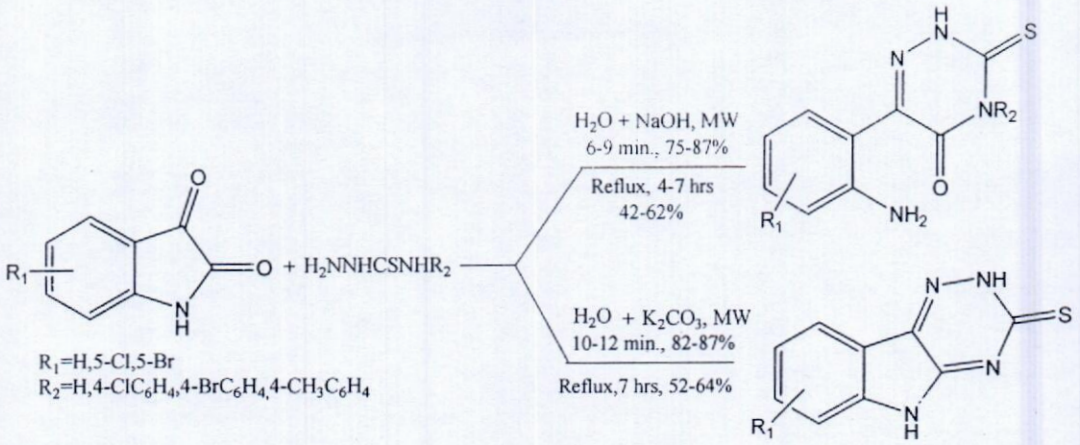
Scheme-I

(II) Dry media one pot solvent free synthesis of N-Mannich bases of isatin under microwave irradiation.

In view of the immense utility of the green synthetic approach, we have also carried out the improved synthesis N-Mannich bases of hexahydro-1H-indole-2,3-dione (5) in Dry Media for the first time under microwave irradiation.

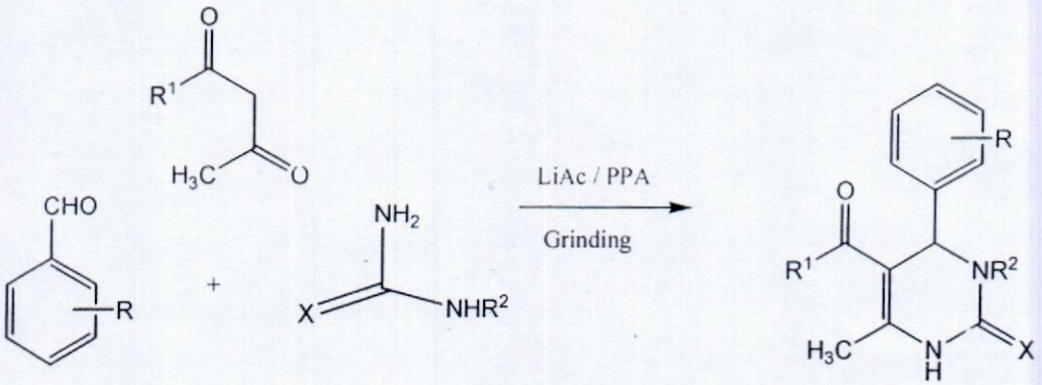
(III) One pot three component condensation reaction in water –An efficient and improved procedure for the synthesis of thioxotriazinones and triazino indole derivatives under microwave irradiation.

We report herein for the first time aqua mediated facile synthesis of novel thioxo[1,2,4]triazin-5(2*H*)-ones and [1,2,4]triazino[5,6-*b*]indoles under microwave irradiation(Scheme-1).



2. Investigation of reaction of aromatic aldehydes, 1, 3-dicarbonyl compound with urea/thiourea/substituted thiourea in the presence of novel catalysts under solvent free condition and cytotoxic activity against the human lung cancer cell line A549 and breast cancer cell line MCF7.

We have reported for the first time a novel, simple and efficient methodology for the synthesis of 3, 4-dihydropyrimidin-2(1*H*)-ones and thiones (DHPM's) by the reaction of aldehydes, 1,3-dicarbonyl compounds, and urea/thiourea using catalytic amount of lithium acetate and PPA (polyphosphoric acid) under solvent free conditions (Scheme-1). Further, comparative catalytic efficiency of lithium acetate and PPA to catalyze Biginelli condensation is also studied under neat conditions.



Scheme-1

6. METHODOLOGY

We have used following methods for the synthesis of some biodynamic heterocyclic compounds:

(A) Microwave Induced Synthesis

(B) Grindstone Technology

(C) Conventional method

(A) Microwave Induced Synthesis

The solvent free microwave-assisted organic reactions can be broadly categorized into two types:

(I) Reactions on solid mineral supports in dry media

This technique was initially described by Keinan and Mazur. Mineral oxides are often very poor conductors of heat but behave as very efficient microwave absorbents, this resulting in turn in a very rapid and homogeneous heating. Consequently, they display very strong specific microwave effects with significant improvements in temperature homogeneity and heating rates enabling faster reactions and less degradation of final products when compared to classical heating.

Aluminas, Silicas, Clays, Zeolites or Envirocates EPZG and EPZ 10 selected as acidic or basic supports[21,22] depending on the type of organic reaction. Alumina alone can possible act as a base towards a rather acidic molecule but if a strong base is necessary, KF on alumina[23] can ionize carbon acidic up to pka~35.

Montmorillonites (clays) such as K10 and KSF offer acidities very close to nitric or sulphuric acids. Envirocates EPZG and EPZ 10 are solid supported catalysts which have Bronsted and Lewis acid characteristics where as EPIC is solid supported strong Bronsted acids, some of the supported reagents, namely clay-supprted iron (III) nitrate (clayfen and copper (II) nitrate (claycop) will also be prepared.

(II) Reaction using neat reactants

These are heterogeneous reactions without any catalyst or support. The simple heterogeneous mixture of the neat reactants can eventually lead to a reaction in which either the solid is partially soluble in the liquid with a reaction occurring in the liquid phase or the liquid is

absorbed on to the surface of the solid with a reaction occurring at the interface. In both situations, the presence of solvent is deleterious due to dilution of the reactants. However, we have developed the facile neat reactions under microwave even if all the reactants are solid.

(B) Grindstone Technology

This technique is superior to the existing methods, since grinding does not require solvents leading to safe and environmental friendly synthesis. Furthermore, the proposed technique does not require external heating or cooling at any stage, leading to energy efficient synthesis providing high yields of products. Such reactions are simple to handle, reduce pollution, comparatively cheaper to operate and may be regarded as more economical and ecologically favourable procedure in chemistry. Generally, Solid-state reactions occur more efficiently and more selectively than does the solution reaction, since molecules in the crystals are arranged tightly and regularly.

(C) Conventional Method

In the conventional method, reactions are carried out by refluxing in various solvents like ethanol, dioxane, toluene, DMF, etc. on various activation modes like water bath, heating mantle, oil bath, etc.

7. RESULTS OBTAINED

The following Series have been completed and published/accepted for publication in the form of research papers.

(A) Paper Published in Journals

1. Aqua mediated facile synthesis of 2-(5/7-fluorinated-2-oxoindolin-3-ylidene)-N- (4-substituted phenyl) hydrazine carbothioamides **2011 RJPBCS Volume 2 Issue 2, 213-219.**
2. Lithium Acetate Mediated Biginelli One-Pot Multi-Component Synthesis Under Solvent Free Conditions and Cytotoxic Activity against the Human Lung Cancer Cell Line A549 and Breast Cancer Cell Line MCF7. **The Scientific World Journal (In Press).**
3. Aqua Mediated One Pot Facile Synthesis of Novel Thioxo-1,2,4-triazin-5(*2H*)-one and [1,2,4]triazino[5,6-*b*]indole Derivatives and their Biological Activities **(Communicated).**

(B) Paper presented/published in conferences

1. Microwave Induced Green Chemical Synthesis of Biodynamic Spiro Indole Derivatives. **National Seminar on *Introduction to Green Chemistry Education: Theory and Practice.* 2010,** Dept. of chemistry, VSSD College (Accredited 'A' Grade by NAAC), Kanpur (U.P).
2. Microwave Accelerated Green Chemical Multicomponent Synthesis Of Novel Heterocycles. **National Seminar on *role of Green Chemistry for risk free environment.* 2010,** Poornima group of college, Jaipur (Raj.) p. 18, Dec. 18, 10.
3. Aqua mediated one pot facile synthesis of thioxo 1,2,4-triazin-5(2H)-one and [1,2,4] triazino [5,6-b] indole derivatives. **3rd International Conference on *HETEROCYCLIC CHEMISTRY* ICHC. 2011,** Rajasthan University, Jaipur. (Accepted for poster presentation).
4. Nanoparticle Mediated One-Pot Multicomponent Facile Synthesis of Dihydropyrimidinones. **The 48th Annual Convention of Chemists organized by the Indian Chemical Society and hosted by the Department of Chemistry, University of Allahabad. 2011,** (Accepted).
5. Synthesis of Shape Controlled ZnO And NiO Nanoparticles and their use in Knoevenagel-**Michael Addition Reactions under Microwave Irradiation. International Conference on *Green Chemistry* (ICGC)-2011,** Central University of Rajasthan Kishangarh (Accepted for poster presentation).

8. CONCLUSIONS

Synthesized compounds were screened for antibacterial activity against bacteria *Bacillus cereus, Enterobacter aerogenes, Escherichia coli, Staphylococcus aureus,* and *K. pneumoniae* by the Agar Well Diffusion method. Most of the compounds were found to be active against bacteria *Bacillus, E coli, S. aureus K. pneumoniae* at 500µg / ml concentration. Compounds were also screened for antifungal activity against *A. alternata* by measuring the zone of inhibition in mm. The antimicrobial activity was performed by cup plate method at concentration 500 µg / ml and 250 µg / ml and some compounds were found to be active against A. *alternata.*

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